

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re PATENT APPLICATION OF

Confirmation No. 4921

Antonio J. GRILLO-LOPEZ et al.

Group Art Unit: 1642

Application Serial No. 09/840,872

Examiner: Susan N. Ungar

Filed: April 25, 2001

Title: INTRATHECAL ADMINISTRATION OF RITUXIMAB FOR TREATMENT OF  
CENTRAL NERVOUS SYSTEM LYMPHOMAS

\* \* \* \* \*

**DECLARATION BY JANE K. RELTON, Ph.D.**

**PURSUANT TO 37 C.F.R. § 1.132**

1. I am a Principal Scientist and Head of the Neuropharmacology Group at Biogen Idec Inc.
2. A copy of my resume is attached.
3. I have reviewed the U.S. Patent No. 6,042,826 to Caliguri et al.
4. I am also familiar with U.S. Patent No. 5,776,456 to Anderson et al.
5. I understand that the Caliguri and Anderson patents were cited in an official action issued by the United States Patent and Trademark Office in connection with U.S. Patent Application No. 09/840,872 entitled "Intrathecal administration of rituximab for treatment of central nervous system lymphomas." I have reviewed the examiner's rejection of claims based on these documents.
6. I further understand that it is the examiner's position that the combined teachings of Caliguri and Anderson render obvious anti-CD20 therapy for the treatment of CNS lymphomas.

7. As described below, I believe that the examiner's analysis fails to consider the unique aspects of treatment of CNS lymphomas and the biological basis for rituximab therapy, which requires immune functions substantial lacking in the CNS.

8. I have reviewed the declaration under 37 CFR 1.132 by Ellen Garber, Ph.D., which was filed on January 12, 2006, in support of the application, and I concur with the comments set forth therein.

9. I understand that in response to Dr. Garber's declaration, the examiner states that she is not persuaded that treatment of CNS lymphomas with rituximab was uncertain prior to the instant invention as no evidence has been presented demonstrating the uncertainty of activity of effector cells in the CNS at the time the invention was made. *See Official Action, April 10, 2006, and Official Action, November 29, 2006*, stating that the claims are rejected for the reasons previously set forth in the paper of April 10, 2006.

10. In response, I wish to initially emphasize that the state of the art has not progressed from a state of certainty at the time of the instant invention, to a state of uncertainty, as described in the declaration by Dr. Garber and further explained by the references cited therein.

11. Rather, Dr. Garber's explanation of the uncertainty in the art of immunotherapy for CNS lymphomas is a more current discussion of the longstanding principle that the CNS is an immunoprivileged site, *i.e.*, a tissue in which immune inhibitory and anti-inflammatory mechanisms physiologically outbalance and counteract immune activity.

12. Accordingly, I attest that the dependence on immune system effector cells, whose activity is limited in the CNS, is one reason why the therapeutic efficacy of anti-CD20 antibodies in the treatment of CNS lymphomas was uncertain prior to the instant invention.

13. As of the priority date of the instant application, it was known that the therapeutic efficacy of rituximab was dependent on the induction of cell-mediated immune responses.

14. In particular, U.S. Patent No. 5,776,456 to Anderson et al. describes that immunologically active anti-CD20 antibodies bind human Clq, mediate complement dependent lysis (CDC) of human B lymphoid cell lines, and lyse human target cells through antibody dependent cellular cytotoxicity (ADCC). *See e.g.*, column 7, lines 16-22.

15. It was also known that the activities of immune effector cells (*i.e.*, dendritic cells, macrophages, and monocytes) mediate significant levels of apoptosis in lymphoma cells using anti-CD20 antibodies.

16. For example, Shan et al. demonstrated that extensive crosslinking of CD20 with anti-CD20 antibodies in the presence of secondary antibodies or FcR-expressing cells induced nuclear DNA fragmentation, leading to apoptotic cell death. *See* Shan et al. *Blood*, 1998, 91: 1644-1652, abstract.

17. To determine whether crosslinking might occur *in vivo* under conditions in which anti-CD20 antibodies are administered to patients, Shan et al. tested whether functional crosslinking of Burkitt's lymphoma cells coated with anti-CD20 antibodies could be achieved by Fc $\gamma$ R-expressing cells. Their results show significant apoptotic induction of Burkitt's lymphoma cells lines in comparison to the level of apoptosis which occurred in the absence of Fc $\gamma$ R-expressing cells (6.05 to 7.35 +/- 0.81% apoptotic nucleic without Fc $\gamma$ R-expressing cells vs. 14.10 +/- 0.39% and 25.30 +/- 0.6% with Fc $\gamma$ R-expressing cells). *See* Shan et al. (1998), page 1648, column 1, paragraph 2.

18. Shan et al. further clarify that FcR-expressing cells contemplated as involved in apoptotic induction include dendritic cells, macrophages and monocytes. *See* Shan et al. *Cancer Immunol Immunother*, 2000, 48:673-683, at 680, column 2, second paragraph.

19. In both studies (Shan et al., 1998; Shan et al. 2000), the authors suggest that *in vivo*, Fc Receptor (FcR)-expressing cells may interact with anti-CD20 antibodies to mediate apoptosis that contributes to the remission observed in clinical trials. See Shan et al. (1998) , page 1649, paragraph bridging columns 1-2. The referenced clinical trials (*i.e.*, Press et al., *Blood*, 1987, 69:584; Maloney et al., *Blood*, 1994, 84:2457; Press et al., *N Engl J Med*, 1993, 329: 1219; Kaminski et al., 1993, *N Engl J Med*, 329: 459) included patients having refractory or relapsed B cell lymphoma, but did not assess the presence and post-treatment response of CNS lymphomas, if present.

20. Notwithstanding this suggestion, it has not been demonstrated that anti-CD20 induction of apoptosis, which occurs at only low levels in the absence of crosslinking, is efficacious for treatment of lymphoma.

21. Rather, it is believed that all three mechanisms, *i.e.*, ADCC, CDC, and apoptosis, contribute to therapeutic efficacy of anti-CD20 antibodies.

22. As of the priority date of the instant application, it was known that the activities of immune effector cells that mediate anti-CD20 induction of ADCC and CDC (natural killer cells and macrophages), as well as FcR-expressing cells that mediate anti-CD20 induction of apoptosis (*e.g.*, dendritic cells, macrophages and monocytes) were substantially compromised or non-existent in the CNS.

23. For example, a review article by Pollack et al., *Seminars in Pediatric Neurology*, 2000, 7(2):131-143, which was published at about the same time as the priority date of the instant application and reflects the state of the art as of the priority date, explains that the unique immunobiological features of the CNS can effect the development of immune effector cells:

[N]ormal neuronal cells exhibit low levels of expression of major histocompatibility complex (MHC) antigen, which are necessary for antigen presentation and lymphocyte activation. In particular, there is a paucity of antigen-presenting cells [APCs], which present antigens in the context of MHC

class II proteins to CD4<sup>+</sup> T-helper cells....In conjunction with binding of co-stimulatory molecules, such as B7, and various cytokines, such as interleukin 1 (IL-1), these T-helper cells are then activated and facilitate development of effector cells. *See*, page 132, column 1, second paragraph.

24. Pollack et al. (2000) further describes the disappointing results obtained when attempts have been made to enhance effector cell activity in the CNS environment, for example, by use of biological response modifiers to potentially drive the growth and differentiation of immune cells and/or activation of effector cells in the CNS. *See* page 134, column 1, second and third paragraphs (general discussion of approach and administration of adjuvants/immunostimulants; page 135, column 1, first paragraph (administration of IFN- $\gamma$ ).

25. Pollack further explains that the immune privilege of the CNS is relative but not absolute:

[T]his immune "privilege is a relative, rather than absolute phenomenon, in that immune responses can be induced to antigens within the brain under appropriate circumstances. Even so, it is clear that the brain constitutes a challenging environment in which to initiate an immune response, a factor that has obvious implications for the application of immunotherapeutic strategies in the treatment of CNS neoplasia." *See* page 132, column 1, first paragraph.

26. In summarizing the results of immunotherapy for CNS lymphoma, Pollack acknowledges that there is substantial unpredictability, notwithstanding the success of immunotherapy in other tissues:

In contrast to the early success that has been achieved in exploiting tumor-associated antigens for immunization in certain tumor types (eg, melanoma), application of this strategy in CNS tumors has been limited. *See* page 139, column 1, last paragraph.

27. In contrast to anti-CD20 antibodies, which induce apoptosis following cross-linking by FcR-expressing cells, U.S. Patent No. 6,042,826 to Caligiuri et al. demonstrates apoptosis in human B lymphoma cells using anti-Fas antibodies in the absence of effector cells. *See*, example 3, page 8, column 8, page 9, columns 9-10 and Figure 3.

28. Therefore, as of the priority date of the instant application, the use of anti-CD20 antibodies for the treatment of CNS lymphomas was unpredictable due in part to the uncertainty of the activity of effector cells in the CNS, notwithstanding the teaching of Caligiuri with respect to anti-Fas antibodies.

29. All statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

April 13<sup>th</sup> 2007

Date



Jane K. Relton, Ph.D.

# **Jane K. Relton, PhD.**

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## **SUMMARY:**

Energetic and accomplished scientist with broad knowledge base and clear strategic vision. Proven management and leadership skills. Extensive experience in neuropharmacology and project leadership. Recognized scientist in the fields of stroke, axonal regeneration and neuroinflammation. Accomplished at establishing and maintaining productive academic collaborations. Proven publication record including patent filings, 14 years experience in drug development. Strong personal interest in public health.

## **EDUCATION:**

University of Manchester, UK. (1989-1992) PhD."Mechanisms of Cerebral Ischaemia"; Wellcome Prize Graduate Studentship  
University of Manchester, UK. (1986-1989) BSc. Pharmacology and Physiology (Joint Honours).

## **PROFESSIONAL EXPERIENCE:**

<i>Head Neuropharmacology Group</i>	2005-present
<i>Principal Scientist</i>	2006-present
<i>Senior Scientist</i>	2002-2006
<i>Scientist II</i>	1999-2002
<u>Biogen Idec, Dept Pharmacology Cambridge MA 02142</u>	

- Hired, trained and currently manage eight+ talented and productive research scientists/ associates working across diverse projects. Group skills include molecular and cellular biology, *in vitro* and *in vivo* pharmacology and neuropathology.
- Lead Pharmacology efforts on all projects requiring neurodegenerative disease models including neuroinflammation, neuropathic pain, axonal regeneration, remyelination, Parkinson's disease.
- Member of internal Scientific Review Committee evaluating all ongoing Neurology research projects.
- Perform due diligence evaluation of licensing opportunities and new technologies, interfacing regularly with members of Business Development and Legal departments.
- Established and oversee collaborations with academic institutions, including supervision of PhD students.
- Designed strategy and implemented Collaborative Inquiry Program across Discovery Research to identify, initiate and manage collaborative research with academic institutes to feed the discovery pipeline.
- Developed/brought in House and run animal models of spinal cord injury, stroke, brain trauma, chemical demyelination and ALS.
- Access transgenic models of neurodegeneration through external academic collaboration (AD, HD, etc.)

- Generated and characterized novel transgenic reporter mice for bioluminescent imaging of specific CNS cell populations. Breed and utilize wide range of knockout and transgenic lines.
- Manage departmental budget and cost center.

*Scientist* 1997-1999  
Eisai London Research Labs., University College London, UK, Pharmacology Group.

- Established and ran rodent models of acute brain injury to evaluate the role of JNK inhibitors in neurodegenerative disease.

*Scientist* 1996-1997  
Cortech Inc, Denver CO; Scientist, Pharmacology Group

- Established and ran rodent models of stroke to evaluate small molecule bradykinin receptor inhibitors as potential therapeutic candidates.

*Post-Doctoral Fellow* 1993-1996  
Synergen Inc./Amgen Inc, Boulder CO, Pharmacology Group

- Established and ran rodent models of global and focal cerebral ischemia
- Contributed to internal effort to determine the physiological and pharmacological effects of trophic factors.
- Worked closely with collaborators at the University of Colorado to evaluate the role of IL-1 in hyperalgesia and sickness behavior.

*Post-Doctoral Fellow* 1992-1993  
Wellcome Prize Post-Doctoral Fellowship, University of Manchester, UK

- Studied the role of IL-1 in the pathogenesis of ischemic and excitotoxic brain damage.

*Summer Intern* 1988  
Dept Microbiology, Ciba-Geigy, Basel, Switzerland

- Established and characterized rodent model of *pneumocystis carinii* infection as part of HIV program.

## **PUBLICATIONS:**

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### **PEER REVIEWED PAPERS:**

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**Relton JK**, Sloan KE, Frew EM, Whalley ET, Adams, SP, Lobb RR. (2001) Inhibition of  $\alpha 4$  integrin protects against transient focal cerebral ischemia in normotensive and hypertensive rats. *Stroke* 32:199-205.

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Martin D., Merkel E, Tucker, K, McManaman J, **Relton JK**, Albert D, Russell DA. (1996). Cachectic effect of ciliary neurotrophic factor in innervated skeletal muscle. *Am. J. Physiol.* **271**:R1422-1428.

**Relton JK**, Martin D, Thompson RC, Russell D. (1996). Peripheral administration of interleukin-1 receptor antagonist inhibits brain damage after focal cerebral ischemia in the rat. *Exp. Neurol.* **138**:206-213.

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**Relton JK**, Rubin LL (1998). Temporal profile of caspase activity and DNA fragmentation in the brain after neonatal hypoxia/ischemia. *Soc Neurosci.* **28**:480.7.

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**Relton JK**, Beckey VE, Whalley ET. (1997). Neuroprotective effect of a selective B<sub>2</sub> receptor antagonist CP-0597, in a rat model of reversible middle cerebral artery occlusion. *Brain '97: J Cereb Blood Flow Metab.*

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## **PATENTS:**

**JK Relton**, M Li, B Ji. Use of Nogo Receptor-1 (NGR1) Antagonists for Promoting Oligodendrocyte Survival (2006).

**JK Relton**, C Mullen, M Scott, C Hession. Methods and products for determining F4/80 gene expression in microglial cells (2005)

**JK Relton**, TM Engber, SM Strittmatter. Treatment of conditions involving dopaminergic neuronal degeneration using Nogo Receptor antagonists (2004)

S Strittmatter, RB Pepinsky, **JK Relton**, L Walus, D. Lee. S. Rabacchi, W-W Li, D. Sah, Nogo Receptor Antagonists (2003)

**JK Relton**, ET Whalley, SP Adams, RR Lobb. Methods of treating central nervous system injury using anti-alpha-4 integrin antagonists. (2000)

ET Whalley, JK Relton. Methods for treating brain injury using bradykinin B<sub>2</sub> receptor antagonists. (1997).

## **INVITED PRESENTATIONS/ORGANIZED SESSIONS**

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- European Winter Conference on Brain Research, Switzerland, 1991
- ICI Link Program, Manchester England, 1992
- Wellcome Prize Student Meeting, London, 1992
- Behavioral Immunology Research Group, University of Colorado, 1994
- CNS injury Conference, University of Pennsylvania, 1995.
- Winter conference on Brain Research, Breckenridge CO, 2000; Mechanisms of brain inflammation after injury. Organizer: J.K. Relton ; Participants: G.J. del Zoppo, J.M. Hallenbeck, N.J. Rothwell.
- Biogen Idec, NeurolInflammation Symposium: Focus on Microglial Cell Biology, 2003; Participants: Hugh Perry, Gary Landreth, Jenny Ting, Monica Carson, Wolfgang Streit.
- Douglas Hospital Research Day, McGill University, Montreal, 2005.
- American Society of Neurochemistry 2006: Workshop on "Identifying Neuronal Glial interactions: new approaches and Insight" Participants: Tony Wyss-Coray, Stanford University, Pedro Lowenstein, UCLA, Salvatore Oddo UC Irvine.
- University of Illinois, Chicago, Dept Anesthesiology "F4/80 GFP/Luc reporter gene expression in mouse microglial cells: A novel system to study microglial activation", July 2006.
- Conference on Wallerian degeneration, Babraham Institute, Cambridge, UK. "The role of Nogo receptor 1 in axonal degeneration in Parkinson's Disease", Sept 2006.
- Gordon Research Conference March 11-16<sup>th</sup> 2007, Glial-Neuronal Interactions, session chair.

## **PROFESSIONAL AFFILIATIONS/RESPONSIBILITIES:**

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Ad Hoc Reviewer for:

- Nature Medicine
- Stroke
- J. Neuroscience
- Neuropharmacology
- J. Cereb. Blood Flow Metab.
- J. Exp. Med.
- Mol. Brain Res.
- Gene Therapy
- Brain Res.

Member of

- American Society for Neuroscience
- American Heart Association, Stroke Council.
- British Neuroscience Association.

- British Pharmacological Society.
- Neurotrauma Society.
- International Society of Neurolimmunology

Fall 2006: Completed "Global Health Challenges (Social Analysis)" Course at Harvard Extension School

Spring 2007: Currently enrolled on course at Mass Biotech Council "An overview of Clinical Research"

#### **UNDER GRADUATE/GRADUATE STUDENT SUPERVISION**

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Supervision of undergraduate/graduate students under the Biogen Idec Summer Intern Program (3month projects):

- 2000: Elizabeth Resendes, Sophomore, MIT
- 2001: Elizabeth Resendes, Junior, MIT
- 2003: Elizabeth Resendes Senior, MIT
- 2004: Rachel Kester Graduate Student, U.Mass, Amherst.
- 2005: Kristen Gorham, Junior, Boston University
- 2006 Tania Sierra, Junior, MIT

Supervision of BBSRC PhD students from the UK (3 month visits to Biogen Idec)

- 2004: Marc Watson, University of Manchester
- 2005: Peter Thornton, University of Manchester
- 2006: Katie Lunnon, University of Southampton

#### **REFERENCES**

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Available on request.